

1 **Title Page**

2 **Title:** Cardiorespiratory fitness predicts clustered cardiometabolic risk in 10-11.9 year olds

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33 **Contributors:** ELH and LMB; wrote and conceived this manuscript. JSB and DB; conceived
34 and designed the Benefits of Fitness Circuits for Primary School Populations. LMB and GS;
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44

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46 **Abstract**

47 The aim of this study was to investigate levels of clustered cardiometabolic risk, and the odds
48 of being 'at risk' according to cardiorespiratory (CRF) fitness status in children. Data from 88,
49 10-11.9 year old children (mean age 11.05 \pm 0.51 years), who participated in either the
50 REACH Year 6 or the Benefits of Fitness Circuits for Primary School Populations studies
51 were combined. Waist circumference, systolic blood pressure (SBP), diastolic blood pressure
52 (DBP), glucose, triglycerides, high-density lipoprotein cholesterol (HDL), adiponectin, and
53 C-reactive protein (CRP) were assessed and used to estimate clustered cardiometabolic risk.
54 Participants were classified as 'fit' or 'unfit' using recently published definitions (46.6
55 mL/kg/min and 41.9 mL/kg/min for boys and girls respectively) and continuous clustered risk
56 scores between fitness groups were assessed. Participants were subsequently assigned to a
57 'normal' or 'high' clustered cardiometabolic risk group based on risk scores, and logistic
58 regression analysis assessed the odds of belonging to the increased cardiometabolic risk
59 group, according to fitness.

60 The unfit group exhibited significantly higher clustered cardiometabolic risk scores ($p <$
61 0.001) than the fit group. A clear association between fitness group and being at increased
62 cardiometabolic risk ($B = 2.509$, $p = 0.001$) was also identified, and participants classed as
63 being unfit were found to have an odds of being classified as 'at risk' of 12.30 (95% CI=
64 2.64-57.33).

65 Assessing cardiorespiratory fitness is a valid method of identifying children most at risk of
66 cardiometabolic pathologies. The ROC thresholds could be used to identify populations of
67 children most at risk, and may therefore be used to effectively target a cardiometabolic risk
68 reducing public health intervention.

69

70 ***Introduction***

71 Adverse cardiometabolic risk factors are associated with an increased risk of cardiovascular
72 disease related morbidity and mortality in adults [12; 24; 29]. Cardiovascular disease is a
73 pathological process that begins in childhood [26], and children with established adverse risk
74 profiles already show markers of sub clinical cardiovascular disease [21]. Cardiometabolic
75 risk factors that originate in childhood and increase the risk of early morbidity and mortality
76 such as obesity, hypertension, insulin resistance and dyslipidaemia track from childhood into
77 adulthood [18; 23]. In the current era when cardiovascular disease associated morbidity and
78 mortality represents a significant disease burden worldwide [20], the early detection of
79 children with increased cardiometabolic risk factors would therefore be extremely beneficial.
80 Such early detection would allow the introduction of targeted interventions aimed at reducing
81 cardiometabolic risk in children and subsequent morbidity.

82 Cardiorespiratory fitness (CRF) is as a key determinant of health and emerging evidence
83 describes a direct relationship between poor CRF and increased cardiometabolic risk in
84 children [4; 5; 13]. Worryingly, levels of CRF have declined in children in recent years,
85 suggesting more children may be at cardiometabolic risk than in previous decades [9]. CRF
86 assessments could offer a valid and pragmatic method of accurately estimating
87 cardiometabolic risk in the paediatric population. Furthermore, CRF has potential as a
88 method of stratifying children into groups that may require further investigation and
89 intervention [1].

90 A recent study by Boddy et al [10] developed ROC generated thresholds for CRF related to
91 obesity in 10-11.9 year old children. The thresholds provided cutpoints for field-assessed
92 CRF, using a 20m multi-stage shuttle runs test, and also detailed equivalent VO_{2peak}
93 thresholds. When the cutpoints were applied in an independent population of adolescents,

94 participants classified as unfit demonstrated significantly increased clustered cardiometabolic
95 risk scores in comparison to those classified as fit [10]. The paper highlighted the potential
96 utility of using CRF values or scores to identify children and adolescents as at increased
97 cardiometabolic risk. To date these thresholds have not been applied to primary-school aged
98 children, or used to calculate the odds of children being classified as ‘at risk’ of
99 cardiometabolic disease. This type of analysis is particularly important as it has the potential
100 to provide a method for identifying children at risk of cardiometabolic disease non-invasively.
101 This would be particularly beneficial in clinical settings where detecting children at risk of
102 cardiometabolic disease as early as possible is vital to facilitate effective, timely and targeted
103 risk reducing intervention. Furthermore, CRF assessments can be conducted on a large scale,
104 therefore offering an opportunity to screen for ‘at risk’ children at the population level.

105 The aim of this study was therefore to investigate levels of clustered cardiometabolic risk and
106 the odds of being ‘at risk’ according to fitness status in 10-11.9 year old schoolchildren
107 classified using published ROC generated CRF thresholds.

108

109 ***Materials and Methods***

110 Data were generated by the REACH Year 6 study based in Liverpool UK and the Benefits of
111 Fitness Circuits for Primary School Populations study based in western Scotland UK.

112

113 ***REACH Y6 Study:***

114 After gaining informed parental consent, participant assent and medical screening 62 10-11.9
115 year old participants agreed to take part in the study in summer 2010. Prior to recruitment
116 institutional ethical approvals for all procedures were received, in addition, Local Research
117 Ethics Committee approvals were received for blood sampling protocols and analysis that

118 involved the local Children's Foundation NHS Trust. Participants attended the laboratories on
119 one occasion to complete assessments of anthropometrics, blood pressure and
120 cardiorespiratory fitness and one school based blood sampling morning.

121

122 *Laboratory Measures:* Stature (Seca Ltd., Birmingham, UK) to the nearest 0.1cm and body
123 mass to the nearest 0.1kg (Seca Ltd. Birmingham, UK) were assessed using standard
124 techniques [22]. Waist circumference (WC) was measured by passing a non-elastic
125 anthropometric tape around the mid-point between the bottom of the ribs and the iliac crest.
126 Blood pressure (BP) was assessed once after a 15 minute rest period with the participant in a
127 supine position (GE DINAMAP ProCare 100-400 Series, UK). Cardiorespiratory fitness
128 (peak oxygen uptake (VO_{2peak})) was assessed using an individually calibrated, continuous
129 incremental treadmill (H P Cosmos, Traunstein, Germany) test to volitional exhaustion using
130 breath by breath gas analysis (Jaeger Oxycon Pro, Viasys Health Care, Warwick, UK). All
131 participants wore a heart rate monitor (Polar, Kempele, Finland) throughout. To account for
132 differences in biological age and limb length, VO_{2peak} test speeds were individually calibrated
133 by anchoring treadmill speeds to set Froude (Fr) numbers. This approach has been described
134 previously, please refer to this reference for further information [17]. Peak VO_2 was defined
135 as the highest 15seconds averaged oxygen uptake achieved during the test when participants
136 reached volitional exhaustion, and the subjective endpoints were met (respiratory exchange
137 ratio > 1.05 and/or HR > 199 beats.min⁻¹).

138 *Blood sampling morning:* Participants attended one blood sampling morning at their school
139 site. After verbal confirmation of overnight fast, samples were drawn from the vena
140 antecubitus by one experienced phlebotomist. Samples were taken between 8.30-10.30am
141 and were transported to the pathology laboratories at the local Children's Foundation NHS
142 Trust for analysis.

143

144 ***Fitness Circuits for Primary School Populations Study:***

145 After gaining informed parental consent and participant assent 55 10-11.9 year old
146 participants were involved in this study, which was conducted in 2011. Prior to recruitment
147 ethical approval was received from the University of the West of Scotland Ethics Committee.
148 Testing sessions occurred on school sites on two separate occasions, all fitness,
149 anthropometric and blood pressure measures were taken on day one, and blood sampling was
150 conducted two days later.

151

152 Stature, was measured to the nearest 0.1 cm (Seca Stadiometer, Seca Ltd, Birmingham, UK).
153 Body mass was measured to the nearest 0.1 kg using calibrated electronic weighing scales
154 (Seca 880, Digital Scales, Seca Ltd, Birmingham, UK). Waist circumference, was measured
155 at the midpoint between the lower ribs and the iliac crest. Blood pressure was measured once
156 with an automated monitor (Omron M10-IT Blood Pressure Monitor HEM-7080IT-E,
157 Omron Healthcare UK Ltd, Milton Keynes, UK) after each participant had sat quietly for a
158 period of 10 min [11]. Cardiorespiratory fitness (CRF) was estimated with the 20 m shuttle
159 run test (20mSRT) [19]. VO_{2peak} was calculated from 20 multi-state shuttle runs
160 performances using previously validated, widely used equations [19].

161

162 *Blood Sampling:* Blood samples were collected between 9:00 am and 11:00 am by two
163 experienced paediatric phlebotomists after an overnight fast in all participants. Blood samples
164 were obtained from an antecubital vein and analyses were subsequently completed within
165 five months of collection.

166

167 ***Clustered Cardiometabolic Risk:***

168 The following variables from both studies were used in the present study to estimate clustered
169 cardiometabolic risk: waist circumference, systolic blood pressure (SBP), diastolic blood
170 pressure (DBP), glucose, triglycerides, high-density lipoprotein cholesterol (HDL),
171 adiponectin, and C-reactive protein (CRP). Data were examined for normality by sex, and
172 the following variables were normalised by log transformation: waist circumference, SBP
173 (boys only), DBP (boys only), glucose (boys only), triglycerides, adiponectin and CRP.
174 Adiponectin and HDL were inverted using a constant of -1, and standardized z-scores were
175 calculated separately by sex for the risk score components. This method of estimating
176 cardiometabolic risk has been used numerous times within pediatric exercise science research,
177 including the European Youth Heart Study [3; 6]. These z-scores were then summed to create
178 a continuous risk score. Selection of risk variables was based on the International Diabetes
179 Federation definition for metabolic syndrome [2], with CRP and adiponectin included as both
180 are potent markers of cardiovascular disease risk [15; 28].

181

182 *Statistical analysis*

183 Participants were classified as 'fit' or 'unfit' using recently published definitions (46.6
184 mL/kg/min and 41.9 mL/kg/min for boys and girls respectively) [10]. Analysis of covariance
185 was completed to assess differences in continuous clustered risk score between the fitness
186 groups, controlling for age and sex. Following ANCOVA analysis, participants were assigned
187 to a 'normal' or 'high' clustered cardiometabolic risk group, with increased risk defined as ≥ 1
188 SD in risk score above the pooled (boys and girls) mean. This method has been used
189 previously in similar aged children [4; 6; 16]. Logistic regression analysis was used to assess
190 the odds of belonging to the increased risk group according to fitness status (low fit vs fit).
191 All analyses were completed using SPSS V20.0 (SPSS Statistics, IBM Corp.), and an alpha
192 value of $p \leq 0.05$ was used to denote statistical significance.

193

194

195 **Results**

196 Eighty-eight participants (42 girls, 46 boys) had complete data for all clustered risk
197 components and VO_{2peak} . Table 1 displays the descriptive characteristics for anthropometrics,
198 VO_{2peak} and risk score components by sex. Girls were less fit, and had higher body mass,
199 body mass index, and triglyceride values than boys.

200

201 TABLE 1 ABOUT HERE.

202

203 In total 18 participants were classed as ‘unfit’ ANCOVA analysis revealed that the unfit
204 group exhibited significantly higher clustered cardiometabolic risk scores in comparison to
205 the fit group after controlling for sex and decimal age (estimated marginal mean risk score fit
206 group = -0.63, SE = 0.37; unfit group mean = 2.74, SE = 0.75; $F = 15.83$, $p < 0.001$) .

207 Participants with a clustered risk score of ≥ 3.25 (unadjusted mean plus 1 SD) were classed as
208 ‘at risk’. Fourteen participants were classified as ‘at risk’. Logistic regression found an
209 association between fitness group and being ‘at risk’ ($B = 2.509$, $p = 0.001$) after controlling
210 for age and sex. For participants classed as unfit, the odds of being classified as ‘at risk’ were
211 12.30 (95% CI= 2.64-57.33) in comparison to those classed as fit.

212

213 **Discussion**

214 The aim of this study was to investigate levels of clustered cardiometabolic risk and the odds
215 of being ‘at risk’ according to fitness status in 10-11.9 year old schoolchildren classified
216 using recently published ROC generated CRF thresholds. Importantly, the results of this
217 study showed that the unfit group ($VO_{2peak} < 46.6$ mL/kg/min and < 41.9 mL/kg/min for boys
218 and girls respectively) exhibited significantly higher clustered cardiometabolic risk scores in
219 comparison to the fit group ($p < 0.001$), and for participants classed as unfit, the odds of

220 being classified as 'at risk' were 12.30 (95% CI= 2.64-57.33). As cardiorespiratory fitness
221 represents the capacity of the respiratory and cardiovascular systems [25], these findings are
222 somewhat intuitive. The association between CRF and clustered cardiometabolic risk likely
223 reflects the broad physiological effects of regular physical activity and adequate CRF
224 including cardiovascular (structural and functional), metabolic (including energy balance)
225 and hormonal parameters [8]. Though some debate exists surrounding fitness levels in
226 children due to the influence of maturation and genetics, it is possible to improve levels of
227 CRF in children if the physical activity stimulus is of sufficient intensity, frequency and
228 duration [7].

229 Increasing cardiometabolic risk in the paediatric population is a global concern [20] and
230 evidence demonstrates that risk factors for cardiometabolic disease track from childhood to
231 adulthood [18]. In order to effectively manage and reduce this public health problem, the
232 introduction of targeted health interventions for the 'at risk' groups are of crucial importance.
233 This is particularly so when the treatment of children exhibiting cardiometabolic risk has
234 been found to be more effective than the treatment of adults [14]. The findings of the present
235 study are of significant clinical importance as they provide further evidence of the strong
236 association between CRF and cardiometabolic disease risk in children. Furthermore, this
237 study lends support to the use of the published CRF thresholds [10] as a method of
238 identifying children at risk of cardiometabolic disease before clinical manifestations are
239 apparent. These data provide a significant contribution towards the development of a valid
240 risk stratification tool to identify children that may benefit from a health intervention aimed at
241 reducing their cardiometabolic risk profile.

242 Clustered cardiometabolic risk scores for children have been successfully calculated in
243 previous studies [3; 6; 16]. Composite risk scores may be more representative of the
244 constellation of disturbances associated with cardiometabolic disease [6], are less sensitive to

245 daily changes in individual risk markers, and may provide a better estimate of risk than
246 individual markers [6; 16]. Despite these advantages, the data required to calculate clustered
247 risk scores are labour intensive, invasive, and costly to obtain, therefore limiting the
248 appropriateness of these scores for assessing risk in children on a large scale. Our findings
249 suggest that CRF provides an accurate representation of cardiometabolic risk that could
250 feasibly be measured on a large scale, for example using a 20m multi-stage shuttle runs test
251 [9; 27].

252 This study is limited by a number of factors. Primarily the data were merged from two studies,
253 and although procedures were very similar across the studies they were not standardised.
254 However, the range of markers included in the study are difficult to assess on a large scale,
255 therefore data were combined for compatible variables to maximise statistical power and
256 ensure these valuable data were utilised to their maximum potential. Secondly, CRF was
257 measured using the 20mSRT in the Fitness Circuits for Primary School Populations and
258 VO_{2peak} was estimated using equations [19], rather than directly assessed via treadmill
259 VO_{2peak} protocol. Despite this the equations used to calculate VO_{2peak} from 20mSRT scores
260 have been widely used and are validated for use in this age-group of children [19].
261 Furthermore, direct assessments of VO_{2peak} require specialised equipment and are time
262 consuming, therefore 20mSRT assessments may be more feasible for use on a large scale.
263 Finally, the composite clustered risk score assumes equal risk rating for each component and
264 1 SD above the mean was used to signify 'at risk'. Whether this value actually represents risk
265 clinically is open to debate, but in the absence of published cut points for clustered
266 cardiometabolic risk this was deemed the most appropriate method and has been previously
267 used in studies assessing clustered cardiometabolic risk in children [4; 6].

268 The major strength of this study is the range of measures included within the clustered risk
269 score, which include emerging risk markers such as adiponectin and CRP, as well as more

270 established functional (BP) and metabolic variables. Furthermore, this is the first study to
271 apply the recently published ROC cutpoints for CRF in similar aged children [10], and lends
272 support to their use as a tool to identify children at risk of cardiometabolic disease. Further
273 studies should aim to develop similar cutpoints across the age-range.

274

275 ***Conclusions***

276 The findings of this study suggest that CRF could potentially be used as a valid method of
277 identifying children most at risk of cardiometabolic pathologies. The ROC thresholds could
278 be used to identify the populations of children who stand to benefit the most from a targeted
279 cardiometabolic risk reducing public health intervention.

280 *Conflicts of Interest*

281 The research team confirm that there are no conflicts of interest for the current study.

282

283 *Acknowledgments*

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288

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375

376

377

378 Table 1. Mean (SD) cardiorespiratory fitness, anthropometric and clustered risk score
 379 components for boys and girls

Measure	Boys	Girls	<i>P</i> Value
Decimal Age (years)	11.08 (0.53)	11.02 (0.49)	0.56
VO _{2peak} (ml/kg/min)	50.39 (5.29)	45.69 (5.69)	< 0.01
Stature (cm)	148.13 (7.25)	148.25 (7.28)	0.94
Body mass (kg)	39.73 (7.73)	44.17 (11.61)	0.03
Body mass index (kg/m ²)	18.09 (2.75)	19.79 (4.27)	0.02
Body mass index SD score	0.31 (1.13)	0.57 (1.35)	0.32
Waist circumference (cm)	61.14 (7.33)	63.50 (9.37)	.17
Systolic BP (mmHg)	115.0 (13.02)	109.61 (14.42)	0.06
Diastolic BP (mmHg)	65.8 (6.42)	63.93 (9.05)	0.25
Glucose (mmol/L)	4.78 (0.42)	4.74 (0.33)	0.64
Triglycerides (mmol/L)	0.56 (0.24)	0.70 (0.33)	0.02
HDL (mmol/L)	1.98 (0.72)	1.77 (0.61)	0.15
CRP (mg/L)	0.60 (1.06)	1.00 (1.33)	0.11
Adiponectin (µg/L)	10.64 (6.88)	9.66 (5.62)	0.46

380

381